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[54]发明名称 取代哌啶-4-酮类化合物的制备

[57]摘要

本发明提供了一种在药物制备中用作中间体的取代哌啶-4-酮类化合物的新制备方法。

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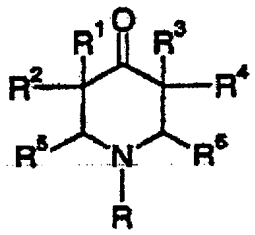
权 利 要 求 书

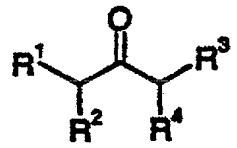
1. 式 I 化合物或其可药用盐的制备方法，



式 I

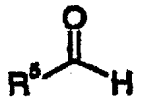
式中 R 是氢、C_1-C_6 烷基、卤代(C_1-C_6)烷基、苯基、苄基、或者被 1-3 个选自 F、Cl、Br、I、C_1-C_6 烷基、C_1-C_6 烷氧基、卤代(C_1-C_6)烷基、苯基、NO_2、和 CN 的取代基取代的苯基；R^1、R^2、R^3、R^4、R^5 和 R^6 各独立地表示氢、C_1-C_6 烷基、卤代(C_1-C_6)烷基、苯基、或者被 1-3 个选自 F、Cl、Br、I、C_1-C_6 烷基、C_1-C_6 烷氧基、-S(C_1-C_6 烷基)、-S(苯基)、卤代(C_1-C_6)烷基、苯基、NO_2、和 CN 的取代基取代的苯基；

该方法包含在合适的酸存在下使式 II 的化合物、式 III 的化合物和式 IV 的化合物化合，接着加入合适的碱和式 V 的化合物，



式 II

式中 R^1、R^2、R^3、和 R^4 定义如上；

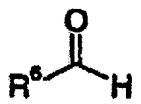


式 III

式中 R^5 定义如上；

$R-NH_2$ 式 IV

式中 R 定义如上；



式 V

式中 R^6 定义如上。

2. 权利要求 1 所述的方法，其中合适的碱是二异丙基乙基胺。

3. 权利要求 2 所述的方法，其中合适的酸是 HCl。

4. 权利要求 3 所述的方法，其中 R^1、R^2、R^3、R^4、R^5 和 R^6 各独立地表示氢、C_1-C_6 烷基、苯基或苄基。

5. 权利要求 4 所述的方法，其中 R^3 和 R^4 表示 C_1-C_6 烷基。

6. 权利要求 4 所述的方法，其中 R^5 表示 C_1-C_6 烷基、R^6 表示氢。

7. 权利要求 5 所述的方法，其中 R^3 和 R^4 表示甲基。

8. 权利要求 6 所述的方法，其中 R^5 表示甲基。

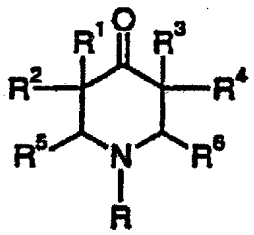
9. 权利要求 7 所述的方法，其中 R^5 和 R^6 表示氢。

10. 权利要求 9 所述的方法，其中 R^1 和 R^2 表示氢。

11. 权利要求 10 所述的方法，其中 R 表示氢。

12. 权利要求 10 所述的方法，其中 R 表示苄基。

13. 式 I 化合物或其可药用盐的制备方法，

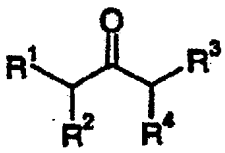


式 I

式中 R 是氢、C_1-C_6 烷基、卤代(C_1-C_6)烷基、苯基、苄基、或者被 1-3 个选自 F、Cl、Br、I、C_1-C_6 烷基、C_1-C_6 烷氧基、卤代(C_1-C_6)烷基、苯基、NO_2、和 CN 的取代基取代的苯基；R^1、R^2、R^3、R^4、R^5 和 R^6 各独立地表示氢、C_1-C_6 烷基、卤代(C_1-C_6)烷基、苯基、或者被 1-3 个选自 F、Cl、Br、I、C_1-C_6 烷基、C_1-C_6 烷氧基、-S(C_1-C_6 烷基)、-S(苯基)、卤代(C_1-C_6)烷基、苯基、NO_2、和 CN 的取代基取代的苯基；

该方法包含在合适的酸存在下使式 II 的化合物、式 III 的化合

物、过量的式 V 的化合物和式 IV 的化合物化合，接着加入合适的碱，

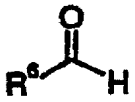


式 II

式中 R^1、R^2、R^3、和 R^4 定义如上；

式 III

式中 R^5 定义如上；



式 V

式中 R^6 定义如上，且 R^6 定义与 R^5 相同，

$R-NH_2$ 式 IV

式中 R 定义如上.

说　明　书

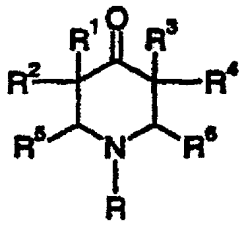
取代哌啶-4-酮类化合物的制备

本发明提供了一种在药物制备中用作中间体的取代哌啶-4-酮类化合物的新制备方法。

G.T.Katvalyan 和 E.A.Mistryukov 在 Izv. Akad. Nauk SSSR, Ser. Khim., 11, 2575(2436transl.)(1968)公开了由甲胺和异丁醛多步骤合成 1-甲基-3,3-二甲基-哌啶-4-酮。另外，I.V.Micovic 等人在 J. Chem. Soc., Perkin Trans., 1, 2041(1996)公开了由苄基胺和丙烯酸甲酯多步骤合成 1-苄基-3,3-偕二甲基-哌啶-4-酮。

现在发现，利用本发明的一罐煮方法可以简单有效地制备 3-取代的哌啶酮类化合物，这就避免了传统的长合成工艺诸如需要迪克曼缩合的麻烦。

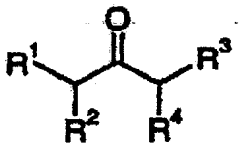
本发明提供了一种式 I 化合物或其可药用盐的制备方法：



式 I

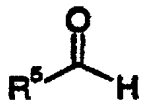
式中 R 是氢、C_1-C_6 烷基、卤代(C_1-C_6)烷基、苯基、苄基、或者被 1-3 个选自 F、Cl、Br、I、C_1-C_6 烷基、C_1-C_6 烷氧基、卤代(C_1-C_6)烷基、苯基、NO_2、和 CN 的取代基取代的苯基；R^1、R^2、R^3、R^4、R^5 和 R^6 各独立地表示氢、C_1-C_6 烷基、卤代(C_1-C_6)烷基、苯基、或者被 1-3 个选自 F、Cl、Br、I、C_1-C_6 烷基、C_1-C_6 烷氧基、-S(C_1-C_6 烷基)、-S(苯基)、卤代(C_1-C_6)烷基、苯基、NO_2、和 CN 的取代基取代的苯基；

该方法包含在合适的酸存在下使式 II 的化合物、式 III 的化合物和式 IV 的化合物化合，接着加入合适的碱和式 V 的化合物，



式 II

式中 R^1、R^2、R^3、和 R^4 定义如上；

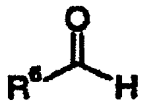


式 III

式中 R^5 定义如上；

$$R-NH_2$$ 式 IV

式中 R 定义如上；



式 V

式中 R^6 定义如上。

本文所用的术语“卤代”、“卤化物”或“卤素”指氯、溴、碘或氟原子，除非另有说明。

本文所用的术语“Me”指甲基，“Et”指乙基，“Pr”指丙基，“iPr”指异丙基，“Bu”指丁基，“Ph”指苯基，“苄基”指 $-CH_2$ 苯基。

本文所用的术语“C_1-C_4 烷基”指直链或支链、一价、1 至 4 个碳原子的饱和脂肪链，包括但不限于甲基、乙基、正丙基、异丙基、正丁基、异丁基等。

本文所用的术语“C_1-C_6 烷基”指直链或支链、一价、1 至 6 个碳原子的饱和脂肪链，包括但不限于甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、正戊基、正己基等。术语“C_1-C_6 烷基”的范围包括了“C_1-C_4 烷基”。

本文所用的术语“C_1-C_6 烷氧基”指直链或支链、连有一个氧原子的 1 至 6 个碳原子的烷基链。典型的 C_1-C_6 烷氧基包括甲氧基、乙氧基、丙氧基、异丙氧基、丁氧基、叔丁氧基、戊氧基等。术语“C_1-C_6 烷氧基”的定义范围包括了“C_1-C_4 烷氧基”。

本文所用的术语“-S(C_1-C_6 烷基)”指直链或支链、连有一个硫原子的 1 至 6 个碳原子的烷基链，例如-SCH_3、-SCH_2CH_3、-$SCH_2CH_2CH_3$、-SCH_2 CH_2 CH_2CH_3 等。

本文所用的术语“卤代(C_1-C_6)烷基”指直链或支链、连有 1、2 或 3 个卤素原子的 1 至 6 个碳原子的烷基链。典型的卤代(C_1-C_6)烷基包括氯甲基、2-溴乙基、1-氯异丙基、3-氟丙基、2,3-二溴丁基、3-氯异丁基、碘代叔丁基、四氟甲基等。术语“卤代(C_1-C_6)烷基”的定义范围包括了“卤代(C_1-C_4)烷基”。

本发明包括式 I 化合物的水合物和可药用盐。本发明的化合物可以具有一个充分的碱性官能团，该官能团能够与任何的许多无机和有机酸反应生成可药用盐。

本文所用的术语“可药用盐”指对活的生物体基本上无毒的式 I 化合物的盐。典型的可药用盐包括通过使本发明的化合物与可药用的无机或有机酸反应所得到的盐。这些盐也叫做酸加成盐。

通常用来生成酸加成盐的酸是无机酸如盐酸、氢溴酸、氢碘酸、硫酸、磷酸等；和有机酸如对甲苯磺酸、甲磺酸、草酸、对溴苯基磺酸、碳酸、琥珀酸、柠檬酸、苯甲酸、乙酸等。这种可药用盐的例子是硫酸盐、焦硫酸盐、硫酸氢盐、亚硫酸盐、亚硫酸氢盐、磷酸盐、磷酸一氢盐、磷酸二氢盐、偏磷酸盐、焦磷酸盐、溴化物、碘化物、醋酸盐、丙酸盐、癸酸盐、辛酸盐、丙烯酸盐、甲酸盐、盐酸盐、二盐酸盐、异丁酸盐、己酸盐、庚酸盐、丙炔酸盐、草酸盐、丙二酸盐、琥珀酸盐、辛二酸盐、癸二酸盐、富马酸盐、马来酸盐、丁炔-1,4-二酸盐、己炔-1,6-二酸盐、苯甲酸盐、氯代苯甲酸盐、甲基苯甲酸盐、羟基苯甲酸盐、甲氧基苯甲酸盐、邻苯二甲酸盐、二甲苯磺酸盐、苯基醋酸盐、苯基丙酸盐、苯基丁酸盐、柠檬酸盐、乳酸盐、g-羟基丁酸盐、甘醇酸盐、酒石酸盐、甲磺酸盐、丙磺酸盐、萘-1-磺酸盐、萘-2-磺酸盐、扁桃酸盐等。优选的可药用酸加成盐是与无机酸如盐酸和氢溴酸生成的盐和与有机酸如马来酸、草酸和甲磺酸生成的盐。

应当承认，形成本发明任何盐的一部分的具体抗衡离子通常并没有严格的要求，只要该盐作为整体是可药用的即可，而且只要该抗衡离子对整个盐没有不利的影响即可。还应当理解，这些盐可以作为水合物存在。

符号“ ▬▬ ”表示从书页平面伸向前面的键。

符号“ ┈┈┈ ”表示从书页平面伸向后面去的键。

本文中，术语“立体异构体”指由相同的键连接并由相同原子组成的化合物，但其三维结构不同而且不能相互转换。该三维结构可以称为构型。本文中，术语“对映体”指两种立体异构体，其分子相互为不能重叠的镜像。术语“手性中心”指连有4个不同基团的碳原子。本文中，术语“非对映体”指不是对映体的立体异构体。另外，仅仅在一个手性中心具有不同构型的两种非对映体在本文中被称为“差向异构体”。术语“外消旋体”、“外消旋混合物”或“外消旋变体”指等份的对映体的混合物。

本文中所用的术语“对映体富集”指一种对映体相对于另一种在数量上增加。表示所达到的对映体富集的通常方法是对映体过量的概念，或“ee”，它由以下等式得到：

$$ee = \frac{E^1 - E^2}{E^1 + E^2} X\ 100$$

式中 E^1 是第一对映体的数量，E^2 是第二对映体的数量。因此如果两种对映体的初始比例是50:50，就像外消旋混合物中存在的那样，所达到的对映体富集足以产生最终比例为50:30，相对于第一对映体的ee是25%。然而，如果最终比例是90:10，相对于第一对映体的ee是80%。优选ee大于90%，更优选ee大于95%，最优选ee大于99%。本领域普通技术人员很容易利用标准的技术和方法确定对映体富集，例如使用带有手性分离柱的气相或者高效液相色谱。合适的手性分离柱、洗脱剂和进行成对对映体分离所需条件的选择是本领域普通技术人员熟知的。另外，本领域普通技术人员利用现有技术公知的标准技术就可以拆分式 I 化合物的对映体，例如 J. Jacques 等人在“Enantiomers, Racemates, and Resolutions”中描述的那些，John

Wiley and Sons, Inc., 1981.

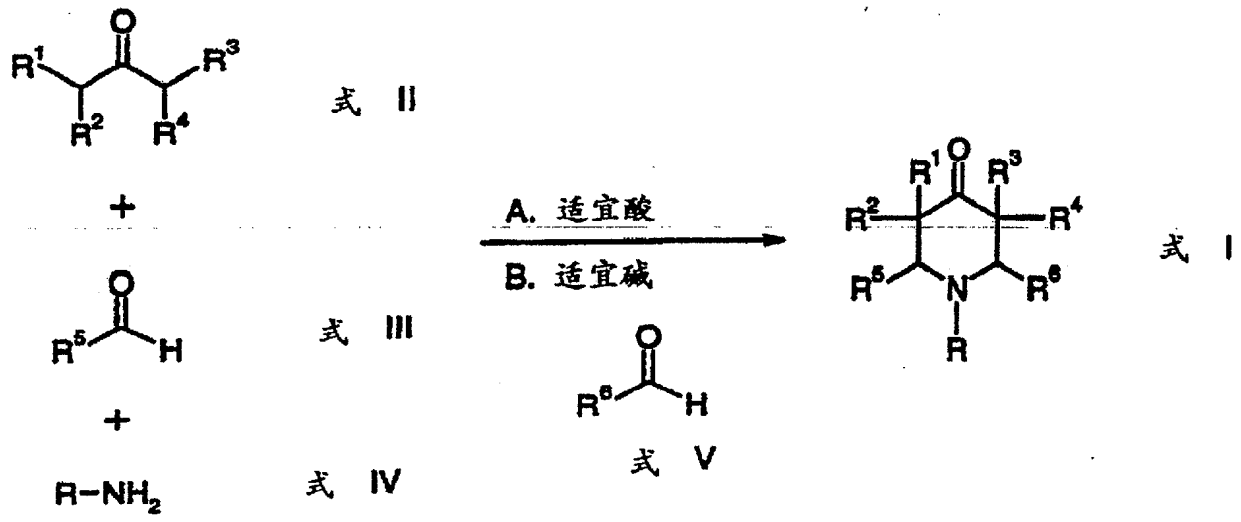
本发明的某些化合物有一或多个手性中心，可以存在许多立体异构体构型．作为这些手性中心的结果，本发明的化合物作为外消旋体、对映体混合物和单独的对映体、以及非对映体和非对映体混合物形式存在．所有这些外消旋体、对映体和非对映体都在本发明的范围中．

术语“R”和“S”在这里就像有机化学中常用的那样表示手性中心的特定构型．术语“R”(rectus)指当沿着朝向最低优先性基团的键的方向看，基团的优先性(最高到次最低)具有顺时针关系的手性中心的构型．术语“S”(sinister)指当沿着朝向最低优先性基团的键的方向看，基团的优先性(最高到次最低)具有逆时针关系的手性中心的构型．基团的优先性基于它们的原子序数(按降低原子序数的次序)．优先性部分列表和立体化学讨论包括在“Nomenclature of the Organic Compounds: Principles and Practice”，(J. H. Fletcher, 等，eds., 1974)，103-120 页．

本领域普通技术人员利用众所周知的技术和方法就可以制备式(I)化合物的特定立体异构体和对映体，例如利用 Eliel 和 Wilen, “Stereochemistry of Organic Compounds”, John Wiley & Sons, Inc., 1994, Chapter 7 Separation of Stereoisomers, Resolution. Racemization, 和 Collet and Wilen, “Enantiomers, Racemates, and Recolutions”, John Wiley & Sons, Inc., 1981 所披漏的内容．例如，利用对映体纯和几何纯或者对映体或几何富集的原料通过立体专一性合成，可以制备特定的立体异构体和对映体．另外，利用例如手性固定相的色谱分离、由用于该目的所使用的试剂所形成的加成盐的酶催拆分或分级重结晶技术，可以拆分和回收特定的立体异构体和对映体．

通过流程 I 所示的方法可以制备式 I 的化合物．该流程并不以任何方式限制本发明的范围．除非另有说明，所有取代基都是先前定义的．试剂和原料是本领域普通技术人员很容易得到的．

流程 I



在流程 I 步骤 A 中，式 IV 的化合物在合适的有机溶剂如乙醇中与式 III 的化合物化合，混合物接着在合适的酸的存在下与式 II 的化合物化合。合适的酸的例子是无机或有机布朗斯台德酸，包括但不限于盐酸、硫酸、磷酸、甲磺酸、甲酸、三氟乙酸、乙酸、氯乙酸等.

例如，约 2.25 当量的式 III 化合物与式 IV 化合物在乙醇中化合. 优选在回流条件下，将该溶液与约 1.0-1.2 当量盐酸在约 50 - 约 90 ℃温度下加入到一种由约 1.05 当量式 II 化合物在乙醇中形成的溶液中. 8 - 约 24 小时后，优选约 18 小时后，在步骤 B 中，加入一种合适的碱，接着加入约 1 当量的式 V 化合物. 合适的碱的例子是众所周知的无机或有机碱，包括但不限于三烷基胺如三乙胺、三丁胺、二异丙基乙胺、异丙基二乙胺、氢氧化钾、氢氧化钠、碳酸钾、碳酸钠、磷酸三钾等。另外，当 $R^5 = R^6$ 时，也可以一次性加入所有的醛. 反应优选在回流条件下于约 50 - 约 80℃温度下搅拌进行约 2 - 约 16 小时.

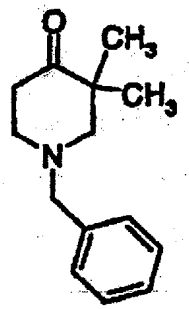
然后利用现有技术中众所周知的技术和方法分离和提纯式 I 的化合物. 例如，将反应混合物冷却到约 5℃，用约 1 当量溶解在水中的碱如氢氧化钾处理. 然后用一种合适的有机溶剂例如庚烷和 MTBE 萃取. 然后合并有机提取物，用无水硫酸镁干燥，过滤并在真空下浓缩，得到式 I 的化合物. 再通过重结晶或快速硅胶色谱(用例如醋酸乙酯/

己烷)作适合的洗脱剂提纯式 I 化合物，得到纯净的式 I 化合物．还可以利用现有技术众所周知的标准技术不用碱处理来分离产物的盐。

下面的实施例表示上述流程 I 一般所述的本发明的方法。这些实施例仅仅用来说明本发明，并不以任何方式限制本发明．试剂和原料都是本领域普通技术人员很容易得到的．这里使用的术语有特定的含义："eq"或"equiv."表示当量；"g"表示克；"mg"表示毫克；"L"表示升；"mL"表示毫升；"μL"表示微升；"mol"表示摩尔；"mmol"表示毫摩尔；"psi"表示磅每平方英寸；"mmHg"表示毫米汞柱；"min"表示分钟；"h"或"hr"表示小时；"℃"表示摄氏度；"TLC"表示薄层色谱；"HPLC"表示高效液相色谱；"R_f"表示保留因子；"R_t"表示保留时间；"δ"表示在四甲基甲硅烷的低磁场的每百万份；"THF"表示四氢呋喃；"DMF"表示 N,N-二甲基甲酰胺；"DMSO"表示二甲亚砜；"LDA"表示二异丙基氨基化锂；"aq"表示含水的；"EtOAc"表示醋酸乙酯；"iPrOAc"表示醋酸异丙酯；"MeOH"表示甲醇；"MTBE"表示叔丁基甲基醚；"TMEDA"表示 N,N,N',N'-四甲基乙二胺；"RT"表示室温。

实施例 1

N-苄基-3,3-二甲基-哌啶-4-酮的制备



合成 I：苄基胺(214g, 2mol)与甲醛(在水中 37%, 375g, 4.5mol)在乙醇(1L)中化合，偶尔冷却．将该两相混合物在 90 分钟内添加到一种由 2-甲基-3-丁酮(182g, 2.11mol)在无水乙醇(1L)和盐酸(209g 37%的溶液，2.1mol)中形成的回流溶液中．将棕色的溶液在回流条件下再加热 18 小时．然后相继加入三乙胺(310ml, 223.8g, 2.21mol)

和甲醛(50g, 36%, 0.6mol)，反应混合物在回流条件下加热24小时。然后使反应混合物冷却到5℃，用氢氧化钾(117.6g, 2.1mol，溶解在200ml水中)处理。再用庚烷(2×500ml)和MTBE(2×500ml)萃取反应混合物。合并有机提取物，用无水硫酸钠干燥，过滤并在真空下浓缩，得到标题化合物(在18%体积的上述合并的有机提取物在浓缩前被取出后得到339.36g)。该物质通过硅胶色谱(用100:1的二氯甲烷/乙醇作洗脱剂)提纯，得到纯净的标题化合物。

^{1}H NMR($CDCl_3$) δ 1.14(s, 6H), 2.41(s, 2H), 2.52(t, 2H), 2.72(t, 2H), 3.57(s, 2H), 7.2-7.4(m, 5H)。

实施例2

N-苄基-3,3-二甲基-哌啶-4-酮的另一种制备方法

将由甲醛(168.5ml, 2.25mol)溶解在500ml无水乙醇中得到的37%（重量）的溶液加入到配备有机械搅拌、加料漏斗和氯化钙干燥管的1升的三颈烧瓶中。得到的溶液在一个冰水浴中冷却到10℃，在1小时时间内滴加苄基胺(109ml, 1mol)。在另一个配备有机械搅拌、加料漏斗和两个冷凝器的3升的三颈烧瓶中加入溶解在500ml无水乙醇中的3-甲基-2-丁酮(113ml, 1.06mol)和浓盐酸(92ml, 1.11mol)。使得到的溶液回流，并在2小时内将甲醛/苄基胺溶液滴入。将溶液回流过夜，然后冷却到环境温度。添加二异丙基乙基胺(142.2g, 1.1mol)和甲醛(22.46ml, 0.3mol)，形成的溶液回流加热6小时，然后冷却到环境温度。用溶解在200ml水中的氢氧化钾(61.6g, 1.1mol)使该溶液停止反应，然后用500ml醋酸乙酯萃取3次。在真空下浓缩有机物，得到225g红色的油。粗油装物溶解在1升二氯甲烷中。将该溶液谨慎地倒在一个烧结玻璃过滤器的1kg硅胶上。用4L二氯甲烷洗涤该硅胶。在真空条件下浓缩二氯甲烷，得到142g黄色的油状物，使其在冷冻器中结晶过夜。产率=65.4%。

上述说明书指出了本发明的一般原则，并用实施例作了详细解释，本领域普通技术人员应当理解，本发明的实施包括所有通常的改变、适应或修改，这些都在所附权利要求书及其等同物的范围内。

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(54) Title: PREPARATION OF SUBSTITUTED PIPERIDIN-4-ONES

(57) Abstract: The present invention provides a novel process for the preparation of substituted piperidin-4-ones useful as intermediates in the preparation of pharmaceuticals.

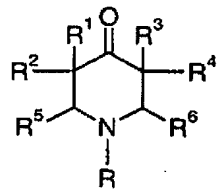
PREPARATION OF SUBSTITUTED PIPERIDIN-4-ONES

The present invention provides a novel process for the preparation of substituted piperidin-4-ones useful as intermediates in the preparation of pharmaceuticals.

G.T. Katvalyan and E.A. Mistryukov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 11, 2575 (2436 transl.) (1968) disclose a multistep synthesis of 1-methyl-3,3-dimethyl-piperidin-4-one starting with methylamine and isobutyraldehyde. In addition, I.V. Micovic, et al., *J. Chem. Soc., Perkin Trans.*, 1, 2041 (1996) disclose a multistep synthesis of 1-benzyl-3,3-gem-dimethyl-piperdine-4-one starting with benzylamine and methyl acrylate.

It has now been discovered that 3-substituted piperidones can be prepared simply and efficiently following the one-pot procedure of the present invention, thus obviating the traditionally lengthy syntheses such as those requiring a Dieckmann condensation.

The present invention provides a process for the preparation of a compound of formula I:



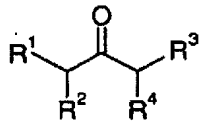
formula I

wherein R is hydrogen, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, phenyl, benzyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo(C_1-C_6)alkyl, phenyl, NO_2, and CN;

R^1, R^2, R^3, R^4, R^5 and R^6 are each independently hydrogen, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, phenyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C_1-C_6 alkyl, C_1-C_6 alkoxy, -S(C_1-C_6 alkyl), -S(phenyl), halo(C_1-C_6)alkyl, phenyl, NO_2, and CN;

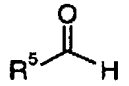
or the pharmaceutically acceptable salt thereof;

comprising combining a compound of formula II:



formula II

wherein R^1, R^2, R^3, and R^4 are defined as above, a compound of formula III:

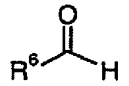


formula III

wherein R^5 is defined as above, and a compound of formula IV:

$R-NH_2$ formula IV

wherein R is defined as above, in the presence of a suitable acid;
followed by addition of a suitable base and a compound of formula V:



formula V

wherein R^6 is defined as above.

As used herein, the terms "Halo", "Halide" or "Hal" refers to a chlorine, bromine, iodine or fluorine atom, unless otherwise specified herein.

As used herein, the term "Me" refers to a methyl group, the term "Et" refers to an ethyl group, the term "Pr" refers to a propyl group, the term "iPr" refers to an isopropyl group, the term "Bu" refers to a butyl group, the term "Ph" refers to a phenyl group, the term "benzyl" refers to a $-CH_2$phenyl group.

As used herein the term "C_1-C_4 alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like.

As used herein the term "C_1-C_6 alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, and the like. The term "C_1-C_6 alkyl" includes within its scope "C_1-C_4 alkyl".

As used herein the term "C_1-C_6 alkoxy" refers to a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom.

Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and the like. The term "C_1-C_6 alkoxy" includes within its definition the term "C_1-C_4 alkoxy".

As used herein the term "-S(C_1-C_6 alkyl)" refers to a straight or branched alkyl chain having from one to six carbon atoms attached to a sulfur atom such as $-SCH_3$, $-SCH_2CH_3$, $-SCH_2CH_2CH_3$, $-SCH_2CH_2CH_2CH_3$, and the like.

As used herein the term "halo(C_1-C_6)alkyl" refers to a straight or branched alkyl chain having from one to six carbon atoms with 1, 2 or 3 halogen atoms attached to it. Typical halo(C_1-C_6)alkyl groups include chloromethyl, 2-bromoethyl, 1-chloroisopropyl, 3-fluoropropyl, 2,3-dibromobutyl, 3-chloroisobutyl, iodo-t-butyl, trifluoromethyl and the like. The term "halo(C_1-C_6)alkyl" includes within its definition the term "halo(C_1-C_4)alkyl".

This invention includes the hydrates and the pharmaceutically acceptable salts of the compounds of formula I. A compound of this invention can possess a sufficiently basic functional group which can react with any of a number of inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of formula I which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid. Such salts are also known as acid addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate,

benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, g-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid, oxalic acid and methanesulfonic acid.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. It is further understood that such salts may exist as a hydrate.

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The designation "  " refers to a bond that protrudes backward out of the plane of the page.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 50:30 is achieved, the ee with respect to the first enantiomer is 25%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the enantiomers of compounds of formula I can be resolved by one of ordinary skill in the art using standard techniques well known in the art, such as those described by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981.

Some of the compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.

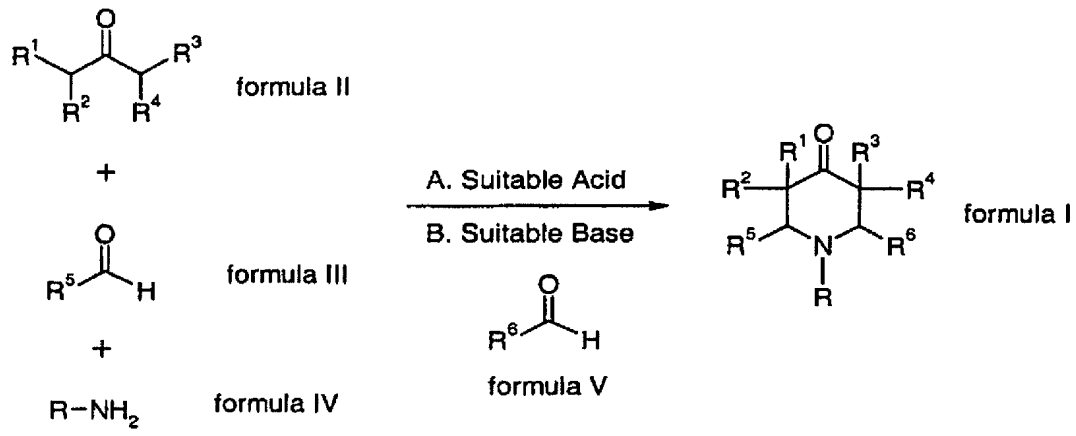
The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing

atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

The specific stereoisomers and enantiomers of compounds of formula (I) can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by Eliel and Wilen, "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, Chapter 7 Separation of Stereoisomers. Resolution. Racemization, and by Collet and Wilen, "Enantiomers, Racemates, and Resolutions", John Wiley & Sons, Inc., 1981. For example, the specific stereoisomers and enantiomers can be prepared by stereospecific syntheses using enantiomerically and geometrically pure, or enantiomerically or geometrically enriched starting materials. In addition, the specific stereoisomers and enantiomers can be resolved and recovered by techniques such as chromatography on chiral stationary phases, enzymatic resolution or fractional recrystallization of addition salts formed by reagents used for that purpose.

Compounds of formula I can be prepared by following the procedures as set forth in Scheme I. This scheme is not intended to limit the scope of the invention in any way. All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

Scheme I



In Scheme I, step A, the compound of formula IV is combined with the compound of formula III in a suitable organic solvent, such as ethanol and the mixture is further combined with a compound of formula II in the presence of a suitable acid. Examples of a suitable acid are inorganic or organic Bronsted acids, which include, but are not limited to, hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, formic acid, trifluoroacetic acid, acetic acid, chloroacetic acid, and the like.

For example, about 2.25 equivalents of a compound of formula III is combined with a compound of formula IV in ethanol. This solution is slowly added to a solution of about 1.05 equivalents of compound of formula II in ethanol with about 1.0 to 1.2 equivalents of hydrochloric acid at a temperature of from about 50 °C to about 90 °C, preferably at reflux. After 8 hours to about 24 hours, preferably about 18 hours, in Step B, a suitable base is added followed by addition of about 1 equivalent of compound of formula V. Examples of a suitable base are inorganic or organic bases well known in the art, which include but are not limited to, trialkylamines, such as triethylamine, tributylamine, diisopropylethylamine, isopropyldiethylamine, potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, potassium phosphate tribasic, and the like. Alternatively, when $R^5 = R^6$, all of the aldehyde can be

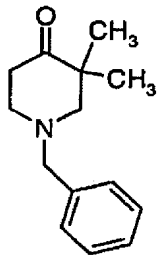
added in one portion. The reaction is stirred at a temperature of from about 50 °C to about 80 °C, preferably reflux, for about 2 hours to about 16 hours.

The compound of formula I is then isolated and purified using techniques and procedures well known in the art. For example, the reaction mixture is cooled to about 5°C and treated with about one equivalent of base, such as potassium hydroxide dissolved in water. The mixture is then extracted with a suitable organic solvent, such as heptane and MTBE. The organic extracts are then combined, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to provide the compound of formula I. The compound of formula I is then purified by recrystallization or flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexane to provide purified compound of formula I. Alternatively, the salt of the product can be isolated using standard techniques well known in the art without treating with base.

The following examples represent the process of the present invention as described generally above in Scheme I. These examples are illustrative only and are not intended to limit the invention in any way. The reagents and starting materials are readily available to one of ordinary skill in the art. As used herein, the following terms have the meanings indicated: "eq" or "equiv." refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "L" refers to liters; "mL" refers to milliliters; "μL" refers to microliters; "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "mm Hg" refers to millimeters of mercury; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ"refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to methyl sulfoxide; "LDA" refers to lithium diisopropylamide; "aq" refers to aqueous; "EtOAc" refers to ethyl acetate; "iPrOAc" refers to isopropyl acetate; "MeOH" refers to methanol; "MTBE" refers to tert-butyl methyl ether; "TMEDA" refers to N,N,N',N'-tetramethylethylenediamine, and "RT" refers to room temperature.

Example 1

Preparation of N-Benzyl-3,3-dimethyl-piperidin-4-one.



Scheme I: Benzylamine (214 g, 2 mol) is combined with formaldehyde (37% in water, 375 g, 4.5 mol) in ethanol (1 L) with occasional cooling. This biphasic mixture is added over a period of 90 minutes to a refluxing solution of 2-methyl-3-butanone (182 g, 2.11 mol) in anhydrous ethanol (1L) and hydrochloric acid (209 g of 37% solution, 2.1 mol). The brownish solution is heated at reflux for an additional 18 hours. Then triethylamine (310 mL, 223.8 g, 2.21 mol) and formaldehyde (50 g, 36%, 0.6 mol) are added sequentially and the reaction mixture is heated at reflux for 24 hours. The reaction mixture is then cooled to 5°C and treated with potassium hydroxide (117.6 g, 2.1 mol, dissolved in 200 mL of water). The reaction mixture is then extracted with heptane (2 X 500 mL) and MTBE (2 X 500 mL). The organic extracts is then combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to provide the title compound, (339.36 g after 18% by volume of the above combined organic extracts was removed prior to concentration). This material was purified by chromatography on silica gel (methylene chloride/ethanol, 100:1) to provide purified title compound.

^{1}H NMR ($CDCl_3$) δ 1.14 (s, 6H), 2.41 (s,2H), 2.52 (t, 2H), 2.72 (t, 2H), 3.57 (s, 2H), 7.2-7.4 (m, 5H).

Example 2

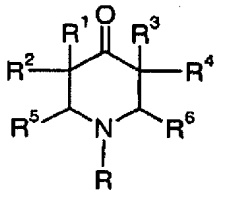
Alternative Preparation of N-Benzyl-3,3-dimethyl-piperidin-4-one.

In a 1 liter 3-necked flask equipped with mechanical stirring, addition funnel and a calcium chloride drying tube is added a 37% weight solution of formaldehyde (168.5 mL, 2.25 mole) dissolved in 500 mL of absolute ethanol. The resulting solution is cooled in an ice-water bath to 10°C, and benzylamine (109 mL, 1mole) is added dropwise over a one hour period. In a separate 3 liter 3-necked flask equipped with mechanical stirring, addition funnel and two condensers is added 3-methyl-2-butanone (113 mL, 1.06mole) dissolved in 500ml of absolute ethanol and concentrated hydrogen chloride (92 mL, 1.11mole). The resulting solution is brought to reflux and the formaldehyde/benzylamine solution is added dropwise over a 2 hour period. This solution is refluxed overnight, and then cooled to ambient temperature. Diisopropylethylamine (142.2 g, 1.1 mole) and formaldehyde (22.46 mL, 0.3mole) are added and the resulting solution is heated to reflux for six hours, and then cooled to ambient temperature. The solution is quenched with potassium hydroxide (61.6 g, 1.1 mole) in 200 mL of water, and then extracted with 500 mL ethyl acetate three times. The organics are concentrated under vacuum to give 225 g of red oil. The crude oil is dissolved in 1 liter of methylene chloride. This solution is carefully poured over 1 kg of silica gel on a sintered glass filter. The silica gel is washed with 4 L of methylene chloride. The methylene chloride is concentrated under vacuum to provide 142 g of a yellow oil which crystallizes in the freezer overnight. Yield=65.4%.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood by one of the ordinary skill in the art, that the practice of the invention encompasses all of the usual variations, adaptations, or modifications, as come within the scope of the following claims and its equivalents.

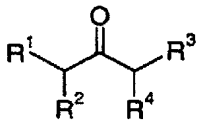
WHAT IS CLAIMED IS:

1. A process for the preparation of a compound of formula I:



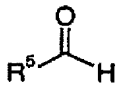
formula I

wherein R is hydrogen, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, phenyl, benzyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo(C_1-C_6)alkyl, phenyl, NO_2, and CN;
R^1, R^2, R^3, R^4, R^5 and R^6 are each independently hydrogen, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, phenyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C_1-C_6 alkyl, C_1-C_6 alkoxy, -S(C_1-C_6 alkyl), -S(phenyl), halo(C_1-C_6)alkyl, phenyl, NO_2, and CN;
or the pharmaceutically acceptable salt thereof;
comprising combining a compound of formula II:



formula II

wherein R^1, R^2, R^3, and R^4 are defined as above, a compound of formula III:

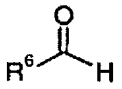


formula III

wherein R^5 is defined as above, and a compound of formula IV:

$R-NH_2$ formula IV

wherein R is defined as above, in the presence of a suitable acid;
followed by addition of a suitable base and a compound of formula V:



formula V

wherein R^6 is defined as above.

2. The process according to claim 1 wherein the suitable base is diisopropylethylamine.

3. The process according to claim 2 wherein the suitable acid is HCl.

4. The process according to claim 3 wherein R^1, R^2, R^3, R^4, R^5 and R^6 are each independently hydrogen, C_1-C_6 alkyl, phenyl or benzyl.

5. The process according to claim 4 wherein R^3 and R^4 are C_1-C_6 alkyl.

6. The process according to claim 4 wherein R^5 is C_1-C_6 alkyl and R^6 is hydrogen.

7. The process according to claim 5 wherein R^3 and R^4 are methyl.

8. The process according to 6 wherein R^5 is methyl.

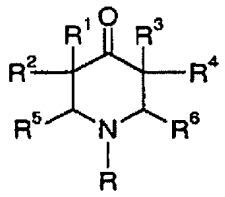
9. The process according to claim 7 wherein R^5 and R^6 are hydrogen.

10. The process according to claim 9 wherein R^1 and R^2 are hydrogen.

11. The process according to claim 10 wherein R is hydrogen.

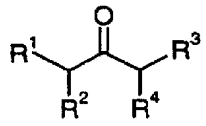
12. The process according to claim 10 wherein R is benzyl.

13. A process for the preparation of a compound of formula I:



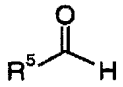
formula I

wherein R is hydrogen, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, phenyl, benzyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo(C_1-C_6)alkyl, phenyl, NO_2, and CN;
R^1, R^2, R^3, R^4, R^5 and R^6 are each independently hydrogen, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, phenyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C_1-C_6 alkyl, C_1-C_6 alkoxy, -S(C_1-C_6 alkyl), -S(phenyl), halo(C_1-C_6)alkyl, phenyl, NO_2, and CN;
or the pharmaceutically acceptable salt thereof;
comprising combining a compound of formula II:



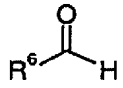
formula II

wherein R^1, R^2, R^3, and R^4 are defined as above, a compound of formula III:



formula III

wherein R^5 is defined as above, an excess of a compound of formula V:



formula V

wherein R^6 is defined as above and R^6 is the same as R^5, and a compound of formula IV:

$R-NH_2$ formula IV

wherein R is defined as above, in the presence of a suitable acid;
followed by addition of a suitable base.